

# On-off intermittency of thalamo-cortical neuronal network oscillations in the electroencephalogram of rodents with genetic predisposition to absence epilepsy

Alexander E. Hramov<sup>a,b</sup>, Vadim V. Grubov<sup>a,b</sup>, Alexey N. Pavlov<sup>b,c</sup>,  
Evgeniya Yu. Sitnikova<sup>d</sup>, Alexey A. Koronovskii<sup>b,e</sup>, Anastasija E. Runnova<sup>b,f</sup>,  
Sveltiana A. Shurugina<sup>e</sup>, Alexey V. Ivanov<sup>b</sup>,

<sup>a</sup>Department of Electronics, Oscillations and Waves, Faculty of Nonlinear Processes,  
Saratov State University, Astrakhanskaya Str. 83, Saratov, 410026, Russia

<sup>b</sup>REC “Nonlinear Dynamics of Complex System”, Saratov State Technical University,  
Politechnicheskaja str, 77, Saratov, 410056, Russia

<sup>c</sup>Radiophysics and Nonlinear Dynamics Chair, Physics Department,  
Saratov State University, Astrakhanskaya Str. 83, Saratov, 410026, Russia

<sup>d</sup>Institute of the Higher Nervous Activity and  
Neurophysiology of Russian Academy of Sciences,  
Butlerova str., 5A, Moscow, 117485, Russia

<sup>e</sup>Department of Physics of Open Systems, Faculty of Nonlinear Processes,  
Saratov State University, Astrakhanskaya Str. 83, Saratov, 410026, Russia

<sup>f</sup>Laboratory of Nonlinear Phenomena of Institute of Natural Science, Saratov State University,  
Astrakhanskaya Str. 83, Saratov, 410026, Russia

## ABSTRACT

Spike-wave discharges are electroencephalographic hallmarks of absence epilepsy. Spike-wave discharges are known to originate from thalamo-cortical neuronal network that normally produces sleep spindle oscillations. Although both sleep spindles and spike-wave discharges are considered as thalamo-cortical oscillations, functional relationship between them is still uncertain. The present study describes temporal dynamics of spike-wave discharges and sleep spindles as determined in long-time electroencephalograms (EEG) recorded in WAG/Rij rat model of absence epilepsy. We have proposed the wavelet-based method for the automatic detection of spike-wave discharges, sleep spindles (10–15 Hz) and 5–9 Hz oscillations in EEG. It was found that non-linear dynamics of spike-wave discharges and sleep spindles fits well to the law of ‘on-off intermittency’. Intermittency in sleep spindles and spike-wave discharges implies that (1) temporal dynamics of these oscillations are deterministic in nature, and (2) it might be controlled by a system-level mechanism responsible for circadian modulation of neuronal network activity.

**Keywords:** Intermittency, neuronal network, wavelet analysis, spike-wave discharges, sleep spindles, EEG, absence epilepsy, pattern recognition

## 1. INTRODUCTION

Sleep spindles (SS) are among the most numerous spontaneous oscillations that are abundantly present in electroencephalograms (EEG) during non-REM sleep in humans and in animals.<sup>1</sup> Sleep spindles can be recorded at the cortical surface, and also in the thalamus as brief episodes of 9–14 Hz oscillations.<sup>2</sup> Thalamo-cortical neuronal circuit, which normally produces SS, under certain conditions could give rise to epileptic spike-wave discharges (SWD).<sup>3</sup> SWD are electroencephalographic hallmarks of generalized idiopathic epilepsies, such as absence epilepsy and other syndromes.

---

Further author information: (Send correspondence to Alexander E. Hramov. E-mail: aeh@nonlin.sgu.ru)

It is well known that sleep spindles and spontaneous SWD are characterized by similar temporal distribution across sleep-waking cycle. Relationship between SWD, SS and mechanisms of sleep is very complicated and it is not well understood.<sup>4</sup> Despite the fact that absence epilepsy common physiological substrate non-sleep, absence seizures might be initiated by wake-related processes (reviewed in Ref.<sup>5</sup>). In particular, in Genetic Rats with Absence Epilepsy (GAERS), “Spike-wave discharges develop from wake-related 5–9 Hz oscillations, which are distinct from spindle oscillations (7–15 Hz)”.<sup>6</sup> 5–9 Hz oscillations originate from the cortex (‘launched by corticothalamic neurons’<sup>6</sup>), in opposite to SS, whose pacemaker is well known to be located in the thalamus.<sup>3</sup> Spontaneous 5–9 Hz oscillations usually present in EEG during awake immobility, but they are not always followed by SWD.<sup>7</sup> Despite considerable progress made in elucidating the cellular mechanisms of 5–9 Hz oscillations, temporal dynamics of these oscillations have not been investigated so far.

This report is devoted to the study of the three kinds of thalamo-cortical oscillatory patterns, SWD, SS and 5–9 Hz oscillations, in respect to their intrinsic time-frequency structure and global dynamics. EEG analysis was performed by means of the continuous wavelet transform. Nonlinear dynamics of SS and SWD was statistically evaluated based on the theory of intermittency. Briefly stated, intermittency in nonlinear systems is known to be associated with aperiodic switching between so-called laminar behavior and turbulent bursts.<sup>8</sup> In EEG, laminar behavior may correspond to long-lasting periods of desynchronized state, and chaotic bursts – to various kinds of oscillatory events. In the human EEG, intermittent behavior is known to characterize dynamics of spontaneous alpha-range activity 8–13 Hz,<sup>9</sup> as well as seizure activity in patients suffering from intractable partial epilepsy.<sup>10</sup> A particular type of intermittent behavior, on-off intermittency, is manifested as abrupt shift between synchronized and desynchronized states in dynamic systems,<sup>11</sup> suggesting that the same intermittent mechanism might underlie temporal dynamics of synchronous thalamo-cortical oscillations in EEG,<sup>12</sup> such as SWD, SS and 5–9 Hz oscillations.

## 2. EXPERIMENTS

EEGs were recorded in six male WAG/Rij rats (one year old). Animals were born and raised at the laboratory of Biological Psychology, Donders Institute for Brain, Cognition and Behavior of Radboud University Nijmegen (The Netherlands). The experiments were conducted in accordance with the legislations and regulations for animal care and were approved by the Ethical Committee on Animal Experimentation of the Radboud University Nijmegen. Distress and suffering of animals were kept to a minimum.

A recording electrode was implanted epidurally over the frontal cortex for the reason that SWD and spindles showed their amplitude maximum in this zone. Ground and reference electrodes were placed over the two symmetrical sides of the cerebellum. EEG recordings were made in freely moving rats continuously during a period of 24 hours. EEG signals were fed into a multi-channel amplifier via a swivel contact, band-pass filtered between 0.5 and 100 Hz, digitized with 1024 samples/s/per channel (CODAS software).

## 3. TIME-FREQUENCY ANALYSIS

Time-frequency characteristics of the investigated phenomena were studied in frontal EEG recordings using continuous wavelet transform (CWT). This analysis was aimed to define the spectral features that would explicitly characterize each class of the investigated EEG patterns; these features were also used as selection criteria in the automatic detection system.

### 3.1. EEG analysis: continuous wavelet transform

Continuous wavelet transform was used for high-resolution representation of EEG signal in time and frequency domains.<sup>13</sup> The CWT,  $W(s, \tau)$ , was obtained by convolving the EEG signal,  $x(t)$ , with wavelet basis function,  $\psi_{s\tau}$ :

$$W(s, \tau) = \frac{1}{\sqrt{s}} \int_{-\infty}^{\infty} x(t) \psi_0 \left( \frac{t - \tau}{s} \right) dt, \quad (1)$$

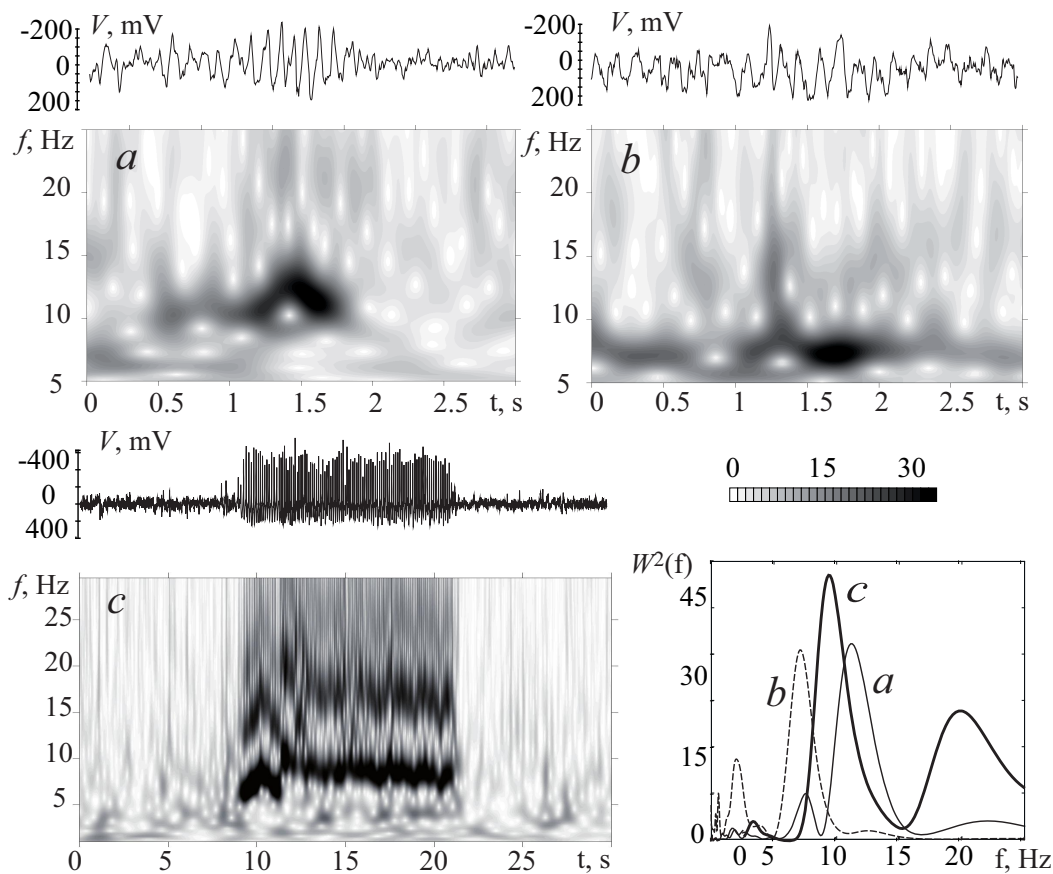
where  $*$  denotes complex conjugation,  $s$  is the time scale, and  $\tau$  is the time shift of CWT. The time scale (or simply *scale*) is inversely proportional to frequency. Complex Morlet wavelet was used as 'mother' wavelet function,

$$\psi_0(\eta) = \frac{1}{\sqrt[4]{\pi}} e^{j4\pi\eta} e^{-\eta^2/2}. \quad (2)$$

Distribution of wavelet energy over the frequency was visually inspected in order to determine the characteristic frequency bands,  $F_s \in (f_1, f_2)$ , that would explicitly characterize SWD, SS and 5–9 Hz oscillations.

$$w(t) = \int_{F_s} |W(f, t)|^2 df. \quad (3)$$

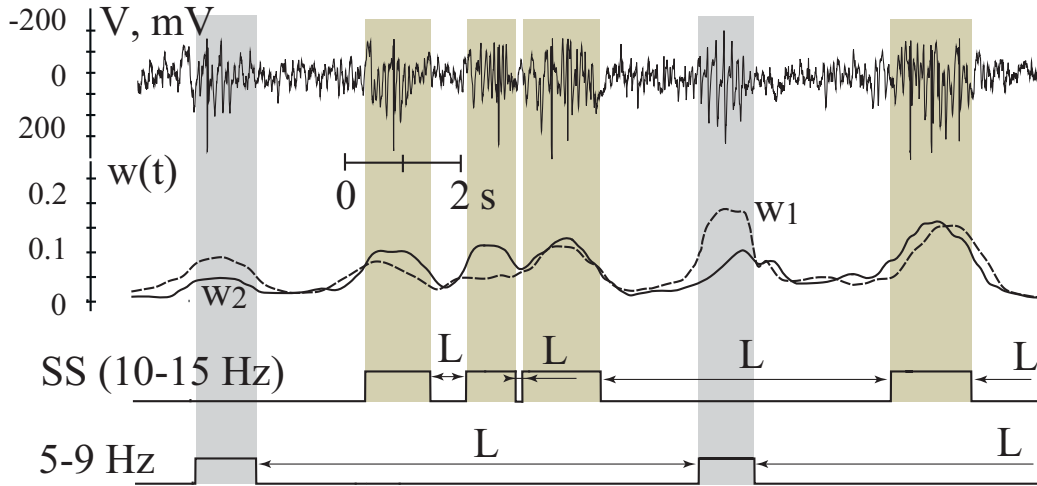
Wavelet power,  $w(t)$ , in specific frequency bands,  $F_s$ , was used in automatic detection system as criteria for selective identification of the investigated EEG patterns.



**Figure 1.** EEG example of typical (a) sleep spindle (10–15 Hz), (b) 5–9 Hz oscillations, and (c) spike-wave discharge and corresponding wavelet spectra. Bottom right plate shows distribution of wavelet energy  $W^2(f)$  as measured in SS (a), 5–9 Hz oscillations (a), and SWD (c), indicating that peak frequencies of these phenomena lie in different clearly distinctive frequency bands

### 3.2. Time-frequency properties of sleep spindles, 5-9 Hz oscillations and SWD

In WAG/Rij rats sleep spindles represented a sequence of 8–14 Hz waves, they were characterized by twofold increase in amplitude as compared to EEG background, had waxing-waning morphology and minimal duration of 0.5 s. According to Morlet-based CWT, SS in WAG/Rij rats showed a marked increase in wavelet power in



**Figure 2.** Principle of automatic detection of SS and 5–9 Hz oscillations in EEG. The top plot illustrates the illustrative examples of the EEG. Curve lines in the middle plot display distribution of wavelet energy  $w_i(t)$  as measured in 5–9 Hz frequency band ( $w_1$ , dotted line) and in 10–15 Hz ( $w_2$ , solid line). The bottom traces demonstrate the result of the detection algorithm for SS and 5–9 Hz oscillations with marked time periods ( $L$ ) between consequent events

10–15 Hz (Fig. 1a). Wavelet spectrum of SS was often contaminated with additional low-frequency components (Fig. 1a) and high-frequency bursts (occasional spikes). There were substantial frequency fluctuations within one spindle train (i.e., intra-spindle frequency variation). Peak frequency of SS varied between 10 and 15 Hz.

Five-9 Hz oscillations (Fig. 1b) characterized by spindle-like waveform. Frequency of these oscillations was lower than that in SS and matched the frequency of epileptic SWD (i.e., 7–9 Hz).

SWD were present in EEG as a sequence of repetitive high-voltage negative spikes and negative waves (Fig. 1c). The envelope of SWD was rectangular due to the presence of large spike components with approximately the same amplitude, and this waveform differed from the waxing-winning waveform of SS (Fig. 1a). In addition to that, spikewave discharges had a longer duration (several seconds) then sleep spindles (0.5–2 s). Wavelet spectrum of SWD usually displayed two dominant frequency components (Fig. 1c):  $\sim 8$ –9 Hz and its harmonics in 16–18 Hz. Sharp spike components of SWD can be recognized in wavelet spectrum as high-frequency bursts (above 20 Hz). Usually, SWD in WAG/Rij rats are preceded by delta and theta precursor activity in cortex and thalamus.<sup>14</sup>

#### 4. DETECTION OF OSCILLATORY PATTERNS IN EEG

Automatic detection system employed specific wavelet-based algorithm described earlier.<sup>15</sup> This method based on measurements of wavelet energy  $w(t)$  in the predetermined frequency bands,  $F_s$ , characteristic for SWD, SS and 5–9 Hz oscillations. The value  $w(t)$  was then compared with the threshold,  $w$ , and the presence of oscillatory pattern was recognized under condition that  $w(t) > w_c$ . This method provided specific discrimination of SWD in background EEG by an increase of cumulative wavelet power in frequency bands  $F_{SWD} \in [8, 14] \& [30, 50]$  Hz. The accuracy of detections was 95–98% in all animals.<sup>16</sup>

Selective detection of SS and 5–9 Hz oscillations in EEG was based on measurements of wavelet energy in two frequency bands,  $F_{s1} \in [5, 9]$  Hz and  $F_{s2} \in [10, 15]$  Hz, correspondingly,  $w_1(t)$  and  $w_2(t)$ . Threshold levels  $w_{1c}$  and  $w_{2c}$  were chosen empirically for  $w_1(t)$  and  $w_2(t)$  correspondingly to provide the most accurate localization of SS in time domain. The presence of a SS was defined if wavelet power in 10–15 Hz,  $w_2(t)$ , exceeded the threshold  $w_{2c}$ , and  $w_2(t)$  was greater than wavelet power in 5–9 Hz,  $w_1(t)$ :

$$w_2(t) > w_{2c} \wedge w_2(t) > w_1. \quad (4)$$

**Table 1.** Amplitude, frequency and threshold parameters counted by wavelet-based algorithm for selective detections of sleep spindles and 5-9 Hz oscillations in EEG of WAG/Rij rats

Rat, ID	5–9 Hz oscillations			Sleep spindles (10–15 Hz)			
	$f$ , Hz	$W_{\max 1}$	$w_{c1}$	$f$ , Hz	$W_{\max 2}$	$w_{c2}$	$w_0$
1	7.2	0.21	0.072	14.1	0.20	0.076	0.031
2	6.4	0.41	0.115	12.6	0.28	0.071	0.028
3	6.1	0.43	0.132	13.2	0.37	0.124	0.034
4	8.3	0.27	0.090	12.8	0.24	0.080	0.025
5	7.4	0.24	0.088	14.0	0.19	0.078	0.028
6	7.8	0.26	0.081	12.1	0.22	0.069	0.024

Here  $f$  is the mean peak frequency of the investigated EEG patterns;  $W_{\max 1}$ ,  $W_{\max}$  are the mean amplitudes of wavelet spectrum in two frequency bands,  $F_{s1} \in [5, 9]$  Hz and  $F_{s2} \in [10, 15]$  Hz;  $w_0$  is the mean wavelet power of background EEG as measured in 10 s interval comprising an investigated oscillatory event;  $w_{1c}$ ,  $w_{2c}$  are the threshold values for wavelet power in 5-9 Hz and 10-15 Hz frequency bands correspondingly.

Five-9 Hz oscillations were identified based on the following condition:

$$w_1(t) > w_{1c} \wedge w_2(t) < w_1. \quad (5)$$

i.e., wavelet power in 5–9 Hz,  $w_1(t)$ , exceeded the threshold  $w_{1c}$ , and  $w_2(t)$  was smaller than wavelet power in 5–9 Hz. The results of automatic detection of SS and 5–9 Hz oscillations are presented in Fig. 2. Table 1 provides information about amplitude and threshold parameters that were used for selective detection of sleep spindles and 59 Hz oscillations in EEG.

Another difficulty encountered in performing automatic selection was the presence of rhythmic alpha/theta components in EEG that were neither associated with sleep spindles nor with 5-9 Hz oscillations. These rhythmic components corresponded to short-term increase of instantaneous wavelet energy in the frequency bands  $F_{s1}$  and  $F_{s2}$  and sometimes caused false detections. In order to prevent incorrect detections, instantaneous wavelet energy,  $w(t)$ , was averaged across time window  $h = 0.5$  s.

$$\bar{w}(t) = \frac{1}{h} \int_{t-h/2}^{t+h/2} w(\tau) d\tau. \quad (6)$$

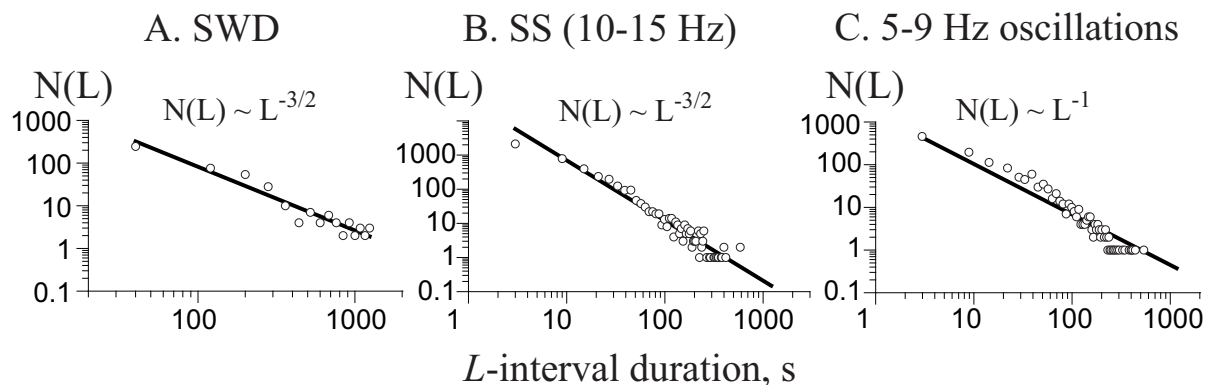
The averaged wavelet energy  $\bar{w}(t)$  was substituted for  $w(t)$  in Eqs. (4) and (5) and this improved quality of automatic detections.

## 5. NONLINEAR DYNAMICS AND ON-OFF INTERMITTENCY OF SWD, SS AND 5–9 HZ OSCILLATIONS

SWD, SS and 5–9 Hz oscillations were automatically detected in EEG using wavelet-based algorithm described in Sec. 4. Temporal dynamics of the investigated oscillatory patterns were examined based on statistical analysis of time periods between consequent EEG events, i.e.,  $L$  intervals, corresponding to the off-phase of intermittent behavior (see Fig. 2 where  $L$ -intervals are marked).

This analysis was performed separately for SWD, SS and 5–9 Hz oscillations. The dependence of the number of off-phases,  $N(L)$ , on their duration,  $L$ , tested for power-law:

$$N(L) = \beta L^\alpha, \quad (7)$$



**Figure 3.** Statistical distribution of time periods between the investigated EEG events ( $L$ -intervals) for one of the studied rats. A, B. In SS and in SWD, distributions of  $L$ -intervals are best approximated to the power law with the exponent  $\alpha = -3/2$  in all individuals. This is typical for on-off intermittency. C. In 5–9 Hz oscillations, distribution of between-spindle intervals fits the power law with the exponent  $\alpha = -1$

where  $\alpha$  is the exponent, and  $\beta$  is a normalization factor. The value of  $\alpha$  in power-law distribution is very important characteristic, since  $\alpha = -3/2$  was proven to hold for a system with on-off intermittency.<sup>8</sup>

Distributions of both between-SWD and between-spindle intervals were close to the straight line in log-log scale in all experimental animals (see for example Fig. 3A,B), corresponding to the power-law with the exponent  $\alpha = -3/2$ :  $N(L) \sim L^{-3/2}$ . This type of distribution is known to be a key feature of on-off intermittency.<sup>17</sup>

The same analysis of 5–9 Hz oscillations showed that distributions of between-oscillation intervals displayed a good approximation to the power law with the exponent  $\alpha = -1$  and were close to the straight line in log-log scale:  $N(L) \sim L^{-1}$  (Fig. 3C). This kind of dynamics was rather uncertain, and it was obviously differed from the on-off intermittent behavior of SS and SWD<sup>18,19</sup>

Although the number of SWD and SS varied from rat to rat, these EEG events were distributed in time in accordance to the power law with the exponent  $-3/2$ . It is important that on-off intermittent behavior was found in both SWD and SS, despite the fact that these EEG events were also differed in respect to their time-frequency profiles (Fig. 1).

## 6. CONCLUSIONS

The present paper demonstrates that distribution of spindle events and spike-wave seizures in EEG is non-random, and that temporal dynamics of these EEG events can be defined as on-off intermittency. This suggests that sleep spindles and SWD, but not 5–9 Hz oscillations, share the same mechanism controlling synchronization in thalamo-cortical neuronal network. In order to produce SWD/SS, thalamo-cortical neuronal network seems to oscillate in the chaotic mode. Furthermore, in systems with on-off intermittency, the onset of each phase is governed by an external driving force.<sup>20</sup> In our case, a high-level hierarchic mechanism might be a 'driven force' that controls processes of synchronization/desynchronization in thalamo-cortical network. This driving mechanism might involve the reticular activating system that modulates excitability of thalamo-cortical neurons and capable of entraining the network in either sleep-related oscillations or in spike-wave paroxysms.<sup>21</sup>

Our results indicate that temporal dynamics of 5–9 Hz oscillations are totally different from that in SWD and sleep spindles. This can be explained by the differences in global network mechanisms, in particular, by the fact that the thalamus does not involved in generation of 5–9 Hz oscillations<sup>6,7</sup> whereas thalamic cellular and network mechanisms are necessary for the initiation of sleep spindle and for the maintenance of SWD<sup>2,3,5</sup>

In general, this report extends nonlinear approach to the temporal dynamics of spontaneous oscillations in EEG and develops the new wavelet-based algorithm for studying several oscillatory patterns in one EEG. Intermittent behavior of synchronous EEG patterns implies that their temporal dynamics are deterministic in nature. Further studies in this field may provide effective tools for predicting epileptic activity.

## ACKNOWLEDGMENTS

We highly appreciate Dr. Gilles van Luijtelaar for providing experimental facilities and WAG/Rij rats in Donders Institute for Brain, Cognition and Behavior. The research has been supported in part by the Russian Foundation for Basic Research (project 12-02-00221) and the Ministry of Education and Science of Russian Federation, projects 14.B37.21.0569 and 14.B37.21.0576.

## REFERENCES

1. L. De Gennaro, M. Ferrara, "Sleep spindles: an overview". *Sleep Med. Rev.* **7** p.423, 2003.
2. M. Steriade, *Neuronal Substrates of Sleep and Epilepsy*. (Cambridge University Press, 2003).
3. M. Steriade et al, "Thalamocortical oscillation in the sleeping and aroused brain". *Science*, **262**, p.679, 1993.
4. G. Kostopoulos, "Spike-and-wave discharges of absence seizures as a transformation of sleep spindles: the continuing development of a hypothesis". *Clin. Neurophysiol. Suppl.*, **2**, p. S27, 2000.
5. D. Pinault, T. O'Brien, "Cellular and network mechanisms of genetically-determined absence seizures". *Thalamus Relat Syst.*, **3**, p. 181, 2005.
6. D. Pinault, A. Slezia, L. Acsady, "Corticothalamic 5–9 Hz oscillations are more pro-epileptogenic than sleep spindles in rats". *J. Physiology*, **574**, p. 209, 2006.
7. D. Pinault, M. Vergnes, C. Marescaux, "Medium-voltage 5–9 Hz oscillations give rise to spike-and-wave discharges in a genetic model of absence epilepsy: in vivo dual extracellular recording of thalamic relay and reticular neurons", *Neurosci.* **105**, p. 181, 2001.
8. N. Platt, E.A. Spiegel, C. Tresser, "On-off intermittency: a mechanism for bursting", *Physical Review Letters*, **70**, p. 279, 1993.
9. P. Gong, A. Nikolaev, C. van Leeuwen, "Intermittent dynamics underlying the intrinsic fluctuations of the collective synchronization patterns in electrocortical activity", *Physical Review E*, **76**, p. 011904, 2007.
10. J. Velazquez, H. Khosravani, A. Lozano, B. Bardakjian, P. Carlen, R. Wennberg, "Type III intermittency in human partial epilepsy", *Eur. J. Neuroscience*, **11**, p. 2571, 1999.
11. S. Boccaletti, D. Valladares. "Characterization of intermittent lag synchronization", *Physical Review E*, **62**, p. 7497, 2000.
12. A.E. Hramov, A.A. Koronovskii, "Intermittent generalized synchronization in unidirectionally coupled chaotic oscillators", *Europhysics Letters*, **70**, p. 169, 2005.
13. A.N. Pavlov, A.E. Hramov, A.A. Koronovskii, E.Yu. Sitnikova, V.A. Makarov, A.A. Ovchinnikov, "Wavelet analysis in neurodynamics", *Physics-Uspekhi*. **55**, p. 9, 2012.
14. van G. Luijtelaar, A.E. Hramov, E.Yu. Sitnikova, A.A. Koronovskii, "Spikewave discharges in WAG/Rij rats are preceded by delta and theta precursor activity in cortex and thalamus", *Clinical Neurophysiology*, **122**, p. 687–695, 2011.
15. E. Sitnikova, A. Hramov, A. Koronovskii, G. van Luijtelaar, "Sleep spindles and spike-wave discharges in EEG: their generic features, similarities and distinctions disclosed with Fourier transform and continuous wavelet analysis", *J. Neurosci. Methods*, **180**, p. 304, 2009.
16. A. Ovchinnikov, A. Luttjohann, A. Hramov, G. van Luijtelaar, "An algorithm for real-time detection of spike-wave discharges in rodents", *J. Neurosci. Methods*, **194**, p. 172, 2010.
17. J. Cabrera, J. Milnor, "On-Off Intermittency in a Human Balancing Task", *Physical Review Letters*, **89**, p. 158702, 2002.
18. A. Hramov, A. Koronovskii, I. Midzyanovskaya, E. Sitnikova, C. van Rijn, "On-off intermittency in time series of spontaneous paroxysmal activity in rats with genetic absence epilepsy", *Chaos*, **16**, p. 043111, 2006.
19. A.A. Koronovskii, G.D. Kuznetsova, I.S. Midzyanovskaya, E.Yu. Sitnikova, D.I. Trubetskov, A.E. Hramov, "Regularities of Alternate Behavior in Spontaneous Nonconvulsive Seizure Activity in Rats", *Doklady Biological Sciences*, **409**, p. 275–277, 2006.
20. Y. Nagai, X. Hua, Y. Lai, "Controlling on-off intermittent dynamics", *Physical Review E*. **54**, p. 1190, 1996.
21. M. Steriade, R. McCarley, *Brainstem control of wakefulness and sleep* (Plenum, New York. 1990).